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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,199	ASTSATUROV ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,11-15,18-22,24-26,28-30 and 32-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,11-15,18-22,24-26,28-30 and 32-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/30/2010 has been entered.

The declaration filed on 09/30/2010 by Neil Berinstein has been considered.

It is noted that "previously cancelled" and ""previously amended" are not a proper claim identifiers (Applicant's attention is directed to 37 CFR 1.121). In this regard, claims 2, 3, 8-10, 16, 17, 23, and 31 should be simply marked as "Canceled". For those claims entered previously that are not currently amended, they should be marked as "Previously presented".

Claims 2-3, 8-10, 16, 17, 23, 27, and 31 are cancelled. Claims 1, 11, 38, and 39 are amended. Claims 1, 4-7, 11-15, 18-22, 24-26, 28-30, 32-39 are pending and currently under examination.

This application 10/690,199 filed on Oct. 21, 2003 claims benefit of provisional application 60/420,425 filed on Oct. 22, 2002. The publication number of this application 10/690,199 is US 2004/0223949 A1, published on Nov. 11, 2004.

Claim Objections

1. Previous objection of claim 37 is **withdrawn** because Applicant has clarified on the record that "1.5" is in fact meant to be "1.5" not "15".

2. Claim 36 remains objected to because of the following informalities: Claim 36 recites "the peptides YLEPGPVTV and IMDQVPFSV". SEQ ID numbers are required for the peptide sequences recited in claim 36, as claims 24, 25, and 26 are written. Appropriate correction is required. Applicant reply filed on 09/30/2010 did not respond to this objection.

Claim Rejection – 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

3. Previous rejection of claims 38 and 39 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is **withdrawn** because the claims have been amended.

Amended claim 38 filed on 09/30/2010 reads as follows: The method of claim 1 wherein the host shows no evidence of melanoma progression following step (b).

Amended claim 39 filed on 09/30/2010 reads as follows: The method of claim 1 wherein the host shows no radiological evidence of melanoma metastases following step (b).

4. Claims 1, 4-7, 11-15, 18-22, 24-26, 28-30, 32-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by claim amendments filed on 09/30/2010.

Amended claim 1 filed on 09/30/2010 reads as follows: A method for treating melanoma comprising: (a) administering to a mammal a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the host develops an immune response against the tumor antigen; and, (b) subsequently administering at least 10 MU/m^2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the mammal; whereby the combination of steps a) and b) provides an enhanced T cell response in the mammal relative to that which occurs following step a) alone.

Claim 1 recites the limitation "the host" in "as the sole active pharmaceutical agent such that the host develops an immune response against the tumor antigen" of step (a). There is insufficient antecedent basis for this limitation in the claim. It is further noted that amended claim 1 simultaneously recites two scopes: "a mammal" and "host". Similarly, claims 36, 38, and 39 depend from claim 1 and also recite "the host". As noted in the office action mailed on 03/31/2010, the limitation "host" recited in claim 1 reads on a mammal (i.e. in vivo) with melanoma as well as an in vitro tissue comprising melanoma.

Claims 4-7, 11-15, 18-22, 24-26, 28-30, 32-39 depend from claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Previous new matter rejection of claims 11 and 12 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is **withdrawn** because Applicant's

remarks (pages 9-10 filed on 09/30/2010) in combination with amendments to the specification field on 09/30/2010 have been fully considered and they are found persuasive.

Claim Rejection – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Previous rejection of claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37-39 under 35 U.S.C. 103(a) as being unpatentable over **Paoletti** (U.S. patent number 5,942,235; issued on August 24, 1999; this reference has been cited in the office action mailed on 07/25/2006) in view of **Emtage et al.** (US 2003/0113919, publication date 06/19/2003, filed on 08/15/2002, provisional applications 60313438, 60313572, 60313573, 60313574 filed on 08/17/2001; this publication has been cited as reference A64 in the IDS filed by Applicant on 03/22/2010), **Kirkwood et al.** (Kirkwood et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. J Clin Oncol. 19(9): 2370-80, 2001; this reference has been cited in the office action mailed on 07/25/2006), and **Aarts et al.** (Aarts et al., Vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity, Cancer Res. 62(20):5770-7, 2002), is **withdrawn** because Applicant's arguments in combination of

declaration by Neil Berinstein field on 09/30/2010 by have been fully considered and they are found persuasive.

Applicant argues that as explained in the attached 37 C.F.R. § 1.131. Declaration of inventor Dr. Neil Berinstein, the claimed method was actually reduced to practice by the inventors prior to the October 15, 2002 publication date of the reference. Applicant states that as explained by Dr. Berinstein in his declaration, he submitted a draft manuscript describing the claimed method (attached to his declaration as Appendix A) to his Sanofi Pastern (at that time named Aventis Pasteur) patens attorney (the undersigned) on July 9, 2010. It is currently maintained as a file on the computer of the undersigned with the time/date of "Tuesday, July 09, 2002, 10:10:12 AM". Applicants maintain that the draft manuscript is evidence of actual reduction to practice prior to the earliest publication date of Aarts. Accordingly, the reference cannot be used in combination with Paoletti, Kirkwood, and Emtage to support a proper prima facie case of obviousness regarding the instantly pending claims. Applicant states that the Office Action does not indicate flint any of Paoietti, Kirkwood, or Fmtage may substitute for Aarts by providing the alleged teaching of vaccine/cytokine combination therapies.

7. Previous rejection of claims 24-26 and 36 under 35 U.S.C. 103(a) as being unpatentable over **Paoletti** (U.S. patent number 5,942,235; issued on August 24, 1999; this reference has been cited in the office action mailed on 07/25/2006) in view of **Emtage et al.** (US 2003/0113919, publication date 06/19/2003, filed on 08/15/2002, provisional applications 60313438, 60313572, 60313573, 60313574 filed on 08/17/2001; this publication has been cited as reference A64 in the IDS filed by Applicant on 03/22/2010), **Kirkwood et al.** (Kirkwood et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. J Clin Oncol. 19(9): 2370-80, 2001; this reference has been cited in the office action mailed on 07/25/2006), and **Aarts et al.** (Aarts et al., Vector-based vaccine/cytokine combination therapy to enhance induction of immune responses to a self-antigen and anti-tumor activity, Cancer Res. 62(20):5770-7, 2002), as applied to claims 1, 4-7,

11-15, 18-22, 28-30, 32-35 and 37-39 above, and further in view of **Kawakami et al.** (Kawakami et al., US Patent No. 5,844,075, issued on 12/01/1998) is **withdrawn** because Applicant's arguments in combination of declaration by Neil Berinstein field on 09/30/2010 by have been fully considered and they are found persuasive.

Applicant states that Dr. Berinstein's 37 C.F.R. § 1. 131 declaration demonstrates that Applicants' claimed invention was reduced to practice prior to Aarts' October 15, 2002 publication date.

The following new grounds of 103 rejections are necessitated by *Applicant's arguments* and the declaration by Neil Berinstein field on 09/30/2010. It is noted that **Morton et al.** (Morton et al., Vaccine therapy for malignant melanoma, CA Cancer J Clin. 46(4):225-44, 1996), instead of previously cited Aarts et al. 2002, has been cited in the following two new grounds of 103(a) rejections to address the limitation subsequently administering interferon alpha 2b (IFN-α2b) in the context of vaccine treatment for melanoma.

8. Claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Paoletti** (U.S. patent number 5,942,235; issued on August 24, 1999; this reference has been cited in the office action mailed on 07/25/2006) in view of **Emtage et al.** (US 2003/0113919, publication date 06/19/2003, filed on 08/15/2002, provisional applications 60313438, 60313572, 60313573, 60313574 filed on 08/17/2001; this publication has been cited as reference A64 in the IDS filed by Applicant on 03/22/2010), **Kirkwood et al.** (Kirkwood et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival

compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. J Clin Oncol. 19(9): 2370-80, 2001; this reference has been cited in the office action mailed on 07/25/2006), and **Morton et al.** (Morton et al., Vaccine therapy for malignant melanoma, CA Cancer J Clin. 46(4):225-44, 1996).

Amended claim 1 filed on 09/30/2010 reads as follows: A method for treating melanoma comprising: (a) administering to a mammal a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the host develops an immune response against the tumor antigen; and, (b) subsequently administering at least 10 MU/m^2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the mammal; whereby the combination of steps a) and b) provides an enhanced T cell response in the mammal relative to that which occurs following step a) alone.

Claim interpretation: The limitation "host" recited in step (a) of claims 1, 38 and 39 reads on a mammal (i.e. in vivo) with melanoma as well as an in vitro tissue comprising melanoma. The limitation "wherein the host shows no evidence of melanoma progression following step (b)" recited in new claim 38 and "wherein the host shows no radiological evidence of melanoma metastases following step (b)" are the consequences following the active steps. The consequences following the active steps are not active steps required for the claimed methods. In this regard, it is further noted that claim 1 does not recite any evidence of melanoma progression before step (b) or recites any radiological evidence of melanoma metastases before step (b).

Paoletti teaches attenuated recombinant viruses containing DNA coding for a cytokine and/or a tumor (or melanoma) associated antigen, as well as methods and compositions employing the viruses. Paoletti teaches that the recombinant viruses can be NYVAC or ALVAC recombinant viruses. The DNA can code for at least one of: human melanoma-associated

antigen (MAGE-1; MZE-2) ; IL-2; IFNγ; IL-4; GMCSF; IL-12; B7; erb-B-2, and carcinoembryonic antigen (CEA). Paoletti teaches that the recombinant viruses and gene products are useful for cancer therapy (See abstract, and lines 40-45, column 13, Paroletti). Paoletti teaches that the immune responses in a mammalian host against tumor cells are mediated by T-cells, particularly cytotoxic T lymphocytes (CTLs); white blood cells capable of killing tumor cells and virus-infected cells (column 7, lines 55-57). Furthermore, Paoletti teaches the administration of a cytokine secreted from modified tumor cells can subsequently be utilized for active immunization. The therapeutic potential for such an administration is based on the ability of cytokines to alter the presentation of TAAs to achieve systematic anti-tumor activity (See column 16, lines 3-8). Paoletti teaches that the vaccines or compositions can be co-administered or sequentially administered with other anti-neoplastic, anti-tumor or anti-cancer agents and/or with agents which reduce or alleviate ill effects of antineoplastic, anti-tumor or anti-cancer agents; again taking into consideration such factors as the age, sex, weight, and condition of the particular patient, and, the route of administration (See line 55-616, column 13, Paroletti)

Paoletti also teaches (1) viral vectors including poxvirus, vaccinia virus, and avipox virus (See, for instances, column 2, background of the invention, second paragraph; claims 1-8); NYVAC, ALVAC, and TROVAC based recombinant viruses expressing TAAs plus or minus specific cytokines for adoptive immunotherapy (See column 15, lines 45-48, column 17, lines 8-9); as well as canarypox virus (column 16, line 55) and fowlpox virus (column 16, line 64); (2) expression of tumor antigens --- CEA, carcinoembryonic antigen, (columns 70-77, example 17); p53 (columns 65-68, example 15); MAGE-1 (columns 68-70, example 16); and cytokines --- human INFγ (columns 83-84, example 21), IL-2 (column 79-80, example 19) in both ALVAC-

based viral vectors (which encompasses ALVAC or ALVAC(2) recited in claim 29-34 of instant application), and NYVAC based viral vectors.

Paoletti does not explicitly teach **(i)** a melanoma-associated tumor antigen or INF-α2b as the sole active pharmaceutical agent recited in amended claim 1, and gp100 peptides recited in newly added claim 36 as the sole active pharmaceutical agent, and **(ii)** subsequently administering at least 10 MU/m^2/day INF-α2b recited in step (b) of claim 1 for cancer vaccine regimen.

(i) Ematge et al. teaches peptides, including tumor-associated antigen gp100, and nucleic acid sequences encoding such peptides for use in diagnosing, treating, or preventing melanoma (See abstract, and paragraph [0010], Ematge et al. 2003). Ematge et al. teaches the following statements: "While the compositions of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other compositions or agents (i.e., other immunogenic targets, co-stimulatory molecules, adjuvants). When administered as a combination, the individual components can be formulated as separate compositions administered at the same time or different times, or the components can be combined as a single composition (See paragraph [0094] by Ematge et al. 2003, which is verbatim of [0074] of 2004/0223949, publication of instant application). Ematge et al. teaches a kit comprising a composition of the present invention is also provided. The kit can include a separate container containing a suitable carrier, diluent or excipient. The kit can also include an additional anti-cancer, anti-tumor or antineoplastic agent and/or an agent that reduces or alleviates ill effects of antineoplastic, anti-tumor or anti-cancer agents for co- or sequential-

administration. Additionally, the kit can include instructions for mixing or combining ingredients and/or administration (See paragraph [0100], Ematge et al. 2003).

(ii) With regard to administering at least 10 MU/m^2/day INF-α2b recited in step (b) of claim 1, and various vaccination of 10 MU/m^2/day INF-α2b recited in claims 18-22, 28, and 29, **Kirkwood et al.** teach high dose INF-α2b, as the sole active pharmaceutical agent administered intravenously, in the treatment of patients with melanoma. Specifically, Kirkwood et al. teach high dose of INF-α2b (20 megaunits [MU]/m^2/d IV (intravenously) x 5 days a week for four week and 10 MU/m^2 SC (subcutaneously) three times per week [TIW] x 48 weeks), which was approved as adjuvant therapy for high-risk melanoma by the United States Food and Drug Administration (FDA) in 1995 (See first paragraph of Introduction, Kirkwood et al., 2001). The treatment significantly prolongs relapse-free survival and overall survival in high-risk melanoma patient. Kirkwood et al. teaches that dose reduction in the INF-α2b was performed in accordance with the common toxicity criteria established by the National Cancer Institute Treatment Evaluation Program. If criteria dictating dose modification were met, then treatment was withheld until recovery from toxicity. Treatment Statistical Analysis was resumed with a 33% dose reduction after the first treatment interruption for toxicity; a 66% dose reduction (i.e. at least 6 MU/m2/day INF-α2b as recited in claim 29 of instant application) was required after a Efficacy comparisons between the GMK and IFNu2b arms were second treatment interruption for toxicity (See bridging paragraph, page 2371-2372, Kirkwood et al., 2001). Kirkwood et al. do not explicitly teach combining high dose INF-α2b cytokine therapy subsequently to nucleic acid expressing a melanoma-associated antigen as a treatment of melanoma.

With regard to subsequently administering of interferon alpha 2b (IFN-α2b) recited in step (b) of claim 1, **Morton et al.** teaches various combinations of vaccine therapy protocols for treating malignant melanoma (See title and abstract, Morton et al., 1996). Morton et al. teaches some immunogenic antigens identified in human melanoma cells (See Table 1, shown below, Morton et al., 1996).

Table 1
Some Immunogenic Antigens Identified in Human Melanoma Cells*

Common Tumor-Associated Antigens (TAA)	Melanoma-Associated Antigens (MAA)
TAA are found not only in melanoma but also in kidney, lung, breast, and other solid neoplasms	MAA are found primarily in melanocytes/melanoma (and rare neoplasms of neural crest origin)
†Urinary TAA (glycoprotein 90)[38]	†Lipoprotein180[15]
†Fetal antigen (glycoprotein 70)[17]	Tyrosinase[22]
†s10 peptide (43 kd)[23]	MART-1/Melan A[26,27]
†MAGE 1[28]	Glycoprotein 75 (gp 75,TRP)[25]
†MAGE 3[21]	Glycoprotein 100 (gp 100/pmel 17)[24,25]
†GM2[16]	High molecular weight melanoma antigen[29,30]
†GD2[16]	
†O-acetyl GD3[16]	
†GM3[15]	

*All of these antigens have been identified in the three melanoma cell lines used in the John Wayne Cancer Institute's living allogeneic melanoma cell vaccine (CancerVax). Some have not yet been fully characterized.

†Antibody responses to these antigens have been demonstrated in the serum of patients receiving active immunotherapy with CancerVax.

Morton et al. teaches that "Other Vaccine Studies in Patients with Stage IV Melanoma: In several phase I/II studies, Mitchell's group tested preparations of two mechanically disrupted melanoma cell lines (Melacine) injected subcutaneously in combination with the adjuvant

DETOX. Median overall survival of the 106 patients was 12.2 months, but 20 patients (19 percent) had objective clinical regression of tumor masses, five with complete responses.42 The median duration of response was 46 months. Clinical response correlated with an increase in the level of cytotoxic T-cell precursors in the blood as well as a partial match of the patient's HLA phenotype with vaccine cell lines" (See bridging paragraph, pages 232-233, Morton et al., 1996). Morton et al. further teaches "Subsequent administration of interferon alfa-2b (IFN α-2b) at a dose of $5x10^6$ U/m2 subcutaneously, three times per week, induced responses in eight of 18 patients who failed Melacine treatment regardless of their HLA phenotype. Based on these results, a national confirmatory phase III trial will compare Melacine plus IFN alfa-2b with IFN alfa-2b alone. This trial will include 300 patients and is scheduled to begin this year" (See right column, page 233, Morton et al., 1996).

It is noted that the combination of the teachings by Paoletti regarding the DNA vaccines or compositions can be co-administered or sequentially administered with other anti-neoplastic, anti-tumor or anti-cancer agents and/or with agents which reduce or alleviate ill effects of antineoplastic, anti-tumor or anti-cancer agents; again taking into consideration such factors as the age, sex, weight, and condition of the particular patient, and, the route of administration (See line 55-616, column 13, Paroletti) and the teachings by Morton regarding "Subsequent administration of interferon alfa-2b (IFN alpha-2b) at a dose of $5x10^6$ U/m^2 subcutaneously, three times per week, induced responses in eight of 18 patients who failed Melacine treatment regardless of their HLA phenotype" render the administration of DNA vaccine recited in step (a) of claim 1 and subsequently administering interferon alpha 2b recited in step (b) of claim 1 prima facie obvious. It is worth noting that Morton et al. teaches that melanoma-associated

antigens (MAA) are weak antigens, and melanoma patients receiving therapeutic vaccines are usually immunized repeatedly for prolonged periods (See right column, page 228, Morton et al., 1996), which provides the motivation for a skilled artisan to use DNA vaccine taught by Paoletti instead of using the cell lysate of mechanically disrupted melanoma cell lines (Melacine) taught by Morton et al.

With regard to absence of repeating step (a) after step (b) recited in claim 35 and step (b) occurs between 1.5 and 17 months after step (a) recited in claim 37, these limitations are optimization of vaccination and obvious variants of the vaccination regimens taught by combined teachings of Morton et al. (See Figures 2 and 3, pages 231-232, Morton et al.) and Kirkwood et al. (See patients and methods, pages 2371-2372, Kirkwood et al.). In this regard, Applicant's attention is directed to the statements provided in MPEP § 2131.03.

2144.05 [R-5] Obviousness of Ranges
See MPEP § 2131.03 for case law pertaining to rejections based on the anticipation of ranges under 35 U.S.C. 102 and 35 U.S.C. 102/103.

II. OPTIMIZATION OF RANGES
A. Optimization Within Prior Art Conditions or Through Routine Experimentation
Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.);

see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable there over because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

B. Only Result-Effective Variables Can Be Optimized

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention to substitute the cytokine (including INFγ and IL-2) taught by combined teachings of Paoletti and Ematge et al., regarding treating melanoma by administering nucleic acid expressing a melanoma-associated antigen gp100, and subsequently administering a high dose INF-α2b taught by Kirkwood et al. and Morton et al., and to follow the melanoma

vaccination treatment regimens taught by Morton et al. and Kirkwood et al. to arrive at the claimed inventions of a method of treating melanoma as recited in claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37-39 of instant application.

One having ordinary skill in the art would have been motivated to substitute the cytokine (including INFγ and IL-2) taught by Paoletti, Emtage et al., and Morton et al. in treating melanoma with a high dose INF-α2b taught by Kirkwood et al., and to follow the cancer vaccination treatment regimens taught by Aarts et al. and Kirkwood et al. because (i) Morton et al specifically teaches subsequent administration of interferon alfa-2b (IFN alpha-2b) at a dose of $5x10^6$ U/m2 subcutaneously, three times per week, induced responses in eight of 18 melanoma patients who failed Melacine treatment regardless of their HLA phenotype, and (ii) Emtage et al specifically teaches peptides, including tumor-associated antigen gp100, and nucleic acid sequences encoding such peptides for use in diagnosing, treating, or preventing melanoma, and the compositions can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other compositions or agents (i.e., other immunogenic targets, co-stimulatory molecules, adjuvants).

There would have been a reasonable expectation of success given (i) combinatory cancer therapy with expression of a melanoma-associated tumor antigen and expression of a cytokine (including INFγ) either co-administered or sequentially administered, by the teachings of Paoletti, (ii) identification of multiple melanoma-associated antigen and expression of nucleic acid encoding the antigens in treating melanoma, by the teachings of Emtage et al. (Examples 1-4), (iii) the results of high dose of INF-α2b in the treatment of melanoma by the teachings of Kirkwood et al to achieve a tumor antigen specific immune response involving enhanced T cell

response, and (iv) various combinations of vaccine therapy protocols for treating malignant melanoma, some immunogenic antigens identified in human melanoma cells, and subsequent administration of interferon alfa-2b (IFN alpha-2b) at a dose of $5x10^6$ U/m^2 subcutaneously, three times per week, induced responses in eight of 18 melanoma patients who failed Melacine treatment regardless of their HLA phenotype, by the teachings of Morton et al. (See title, Table 1, and page 233).

Thus, the claimed invention as a whole was clearly prima facie obvious.

9. Claims 24-26 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Paoletti** (U.S. patent number 5,942,235; issued on August 24, 1999; this reference has been cited in the office action mailed on 07/25/2006) in view of **Emtage et al.** (US 2003/0113919, publication date 06/19/2003, filed on 08/15/2002, provisional applications 60313438, 60313572, 60313573, 60313574 filed on 08/17/2001; this publication has been cited as reference A64 in the IDS filed by Applicant on 03/22/2010), **Kirkwood et al.** (Kirkwood et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. J Clin Oncol. 19(9): 2370-80, 2001; this reference has been cited in the office action mailed on 07/25/2006), and **Morton et al.** (Morton et al., Vaccine therapy for malignant melanoma, CA Cancer J Clin. 46(4):225-44, 1996), as applied to claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37-39 above, and further in view of **Kawakami et al.** (Kawakami et al., US Patent No. 5,844,075, issued on 12/01/1998).

The teachings of Paoletti, Emtage et al., Kirkwood et al., and Morton have been discussed in the preceding section of the rejection of claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37-39 under 35 U.S.C. 103(a) as being unpatentable over Paoletti in view of Emtage et al., Kirkwood et al., and Morton et al. It is noted the limitations recited in new claim 36 are obvious variant of the teachings by Morton et al. regarding various subsequent booster vaccinations with a melanoma-associated tumor antigen, which includes gp100 taught by Emtage et al. and Morton et al., and/or a cytokine.

None of Paoletti, Emtage et al., Kirkwood et al. and Morton et al. teaches SEQ ID No:2 and SEQ ID No:3 of gp100 recited in claims 24-26 and 36.

However, at the time of filing of instant application, the gp100 as a melanoma-associated tumor antigen recited in claims 11-13 and 23, and SEQ ID No:2 and SEQ ID No:3 of gp100 recited in claims 24-26, were known in the art. For instant, **Kawakami et al.** teaches immunogenic peptides derived from melanoma antigen designated gp100, including SEQ ID No: 2 and SEQ ID No: 3 recited in claims 24-26 and 36 of instant application (See below for the alignment of SEQ ID No: 2 of instant application with SEQ ID No: 84 of Kawakami et al., and the alignment of SEQ ID No: 3 of instant application with SEQ ID No: 104 of Kawakami et al.).

SEQ ID No: 2

```
RESULT 1
US-08-417-174-84
; Sequence 84, Application US/08417174
; Patent No. 5844075
;  GENERAL INFORMATION:
;     APPLICANT:  KAWAKAMI, YUTAKA; ROSENBERG,
;     APPLICANT:  STEVEN A.
;     TITLE OF INVENTION:  MELANOMA ANTIGENS AND
;     TITLE OF INVENTION:  THEIR USE IN DIAGNOSTIC AND THERAPEUTIC
;     TITLE OF INVENTION:  METHODS
;     NUMBER OF SEQUENCES:  126
;     CORRESPONDENCE ADDRESS:
;       ADDRESSEE:  MORGAN & FINNEGAN, L.L.P.
```

```
;      STREET:  345 PARK AVENUE
;      CITY:  NEW YORK
;      STATE:  NEW YORK
;      COUNTRY:  USA
;      ZIP:  10154
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  FLOPPY DISK
;      COMPUTER:  IBM PC COMPATIBLE
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  ASCII
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/417,174
;      FILING DATE:  05-APR-1995
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/231,565
;      FILING DATE:  22-APR-1994
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  CAROL M. GRUPPI
;      REGISTRATION NUMBER:  37,341
;      REFERENCE/DOCKET NUMBER:  2026-4124US1
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (212) 758-4800
;      TELEFAX:  (212) 751-6849
;      TELEX:  421792
;  INFORMATION FOR SEQ ID NO:  84:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  9
;      TYPE:  amino acid
;      STRANDEDNESS:  Unknown
;      TOPOLOGY:  Unknown
;    MOLECULE TYPE:  Peptide
US-08-417-174-84

  Query Match           100.0%;  Score 45;  DB 1;  Length 9;
  Best Local Similarity  100.0%;  Pred. No. 1e+06;
  Matches    9;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 IMDQVPFSV 9
              |||||||||
Db          1 IMDQVPFSV 9
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SEQ ID No:3

```
RESULT 1
US-08-417-174-104
; Sequence 104, Application US/08417174
; Patent No. 5844075
;  GENERAL INFORMATION:
;    APPLICANT:  KAWAKAMI, YUTAKA; ROSENBERG,
;    APPLICANT:  STEVEN A.
;    TITLE OF INVENTION:  MELANOMA ANTIGENS AND
;    TITLE OF INVENTION:  THEIR USE IN DIAGNOSTIC AND THERAPEUTIC
;    TITLE OF INVENTION:  METHODS
;    NUMBER OF SEQUENCES:  126
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  MORGAN & FINNEGAN, L.L.P.
;      STREET:  345 PARK AVENUE
;      CITY:  NEW YORK
;      STATE:  NEW YORK
;      COUNTRY:  USA
;      ZIP:  10154
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  FLOPPY DISK
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;      COMPUTER:  IBM PC COMPATIBLE
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  ASCII
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/417,174
;      FILING DATE:  05-APR-1995
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/231,565
;      FILING DATE:  22-APR-1994
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  CAROL M. GRUPPI
;      REGISTRATION NUMBER:  37,341
;      REFERENCE/DOCKET NUMBER:  2026-4124US1
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (212) 758-4800
;      TELEFAX:  (212) 751-6849
;      TELEX:  421792
;  INFORMATION FOR SEQ ID NO:  104:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  9
;      TYPE:  amino acid
;      STRANDEDNESS:  Unknown
;      TOPOLOGY:  Unknown
;    MOLECULE TYPE:  Peptide
US-08-417-174-104

  Query Match           100.0%;  Score 49;  DB 1;  Length 9;
  Best Local Similarity  100.0%;  Pred. No. 1e+06;
  Matches    9;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 YLEPGPVTV 9
              |||||||||
Db          1 YLEPGPVTV 9
```

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Kawakami et al. regarding the DNA encoding immunogenic peptides derived from melanoma antigen gp100, including SEQ ID No: 2 and SEQ ID No:3 recited in claims 24-26 and 36 of instant application, into the combined teachings of Paoletti, Emtage et al., Kirkwood et al., and Morton et al. directing to a method for treating melanoma comprising : (a) administering to a mammal a comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the mammal develops an immune response against the melanoma-associated tumor antigen; and (b) subsequently administering at least 10 MU/m^2/day INF-α2b as the sole active pharmaceutical agent to the mammal, whereby the combination of step (a) and (b) provides an enhanced T cell

response in the mammal relative to that which occurs of following step (a), to arrive at the claimed inventions as recited in claims 24-26 and 36.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Kawakami et al. on the DNA encoding DNA encoding immunogenic peptides derived from melanoma antigen gp100, including SEQ ID No: 2 and SEQ ID No: 3, into the combined teachings of Paoletti, Emtage et al., Kirkwood et al., and Morton et al. because Kawakami et al. teaches that gp100 is a well-established melanoma tumor antigen and SEQ ID No: 2 and SEQ ID No: 3 are immunogenic to induce anti-melanoma T cells mediated immune response.

There would have been a reasonable expectation of success given (i) combinatory cancer therapy with expression of a tumor antigen and expression of a cytokine (including INFγ) either co-administered or sequentially administered, by the teachings of Paoletti, (ii) identification of multiple melanoma-associated antigen and expression of nucleic acid encoding the antigens in treating melanoma, by the teachings of Emtage et al. (Examples 1-4), (iii) the results of high dose of INF-α2b in the treatment of melanoma by the teachings of Kirkwood et al. to achieve a tumor antigen specific immune response involving enhanced T cell response, (iv) various combinations of vaccine therapy protocols for treating malignant melanoma, immunogenic antigens identified in human melanoma cells, and subsequent administration of interferon alfa-2b (IFN alpha-2b) at a dose of $5x10^6$ U/m^2 subcutaneously, three times per week, induced responses in eight of 18 melanoma patients who failed Melacine treatment regardless of their HLA phenotype, by the teachings of Morton et al. (See title, Table 1, and page 233), and (v)

generation of cytotoxic T lymphocytes (CTL) immune response by administering nucleic acid encoding gp100, by the teachings of Kawakami et al. (See Example 3)

Thus, the claimed invention as a whole was clearly prima facie obvious.

Applicant's arguments and ***Response to Applicant's arguments***

Applicant's remarks regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above. It is noted that **(i)** previous rejection of claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37-39 under 35 U.S.C. 103(a) as being unpatentable over Paoletti in view of Emtage et al., Kirkwood et al. and Aarts et al. has been withdrawn, and **(ii)** previous rejection of claims 24-26 and 36 under 35 U.S.C. 103(a) as being unpatentable over Paoletti in view of Emtage et al., Kirkwood et al. and Aarts et al., as applied to claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37-39 above, and further in view of Kawakami et al. has been withdrawn.

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc. that forecloses the argument that a specific teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) [available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf; and KSR Guidelines Update has been published in the Federal Register at 75 Fed. Reg. 53643-60 (Sep. 1, 2010) and is posted at USPTO's internet Web site at http://www.uspto.gov/patents/law/notices/2010.jsp]. The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc., the suggestion and motivation to combine Paoletti, Emtage et al., Kirkwood et al., and **Morton et al.** (and Kawakami et al. for rejection of claims 24-26 and 36) have been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

10. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632